DOCUMENT NUMBER: PREV199800122032
TITLE: Dermatology 1997: Immunointervention on the advance.
AUTHOR(S): Burg, G. (1)
CORPORATE SOURCE: (1) Dermatol. Klin., Universitaetsspital, Cloriastrasse 31,
CH-8091 Zuerich Switzerland
SOURCE: Schweizerische Medizinische Wochenschrift, (Jan. 6, 1998) Vol. 128, No. 1-2, pp. 18-20.
ISSN: 0036-7672.
DOCUMENT TYPE: Article
LANGUAGE: German

L3 ANSWER 39 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:111639 CAPLUS
DOCUMENT NUMBER: 126:170381
TITLE: Method induction of antigen-specific immune tolerance
INVENTOR(S): Beschorner, William E.
PATENT ASSIGNEE(S): Beschorner, William E., USA
SOURCE: U.S., 12 pp., Cont.-in-part of U.S. Ser. No. 940,640, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5597563	A	19970128	US 1995-573648	19951218
PRIORITY APPLN. INFO.:			US 1992-940640	19920904

AB A method for inducing antigen-specific immune tolerance by depletion of resident thymic **antigen presenting** cells (APCs) and re-population of thymus with new APCs contg. the antigen for tolerance is described. The antigen is an alloantigen, xenoantigen or autoantigen, and the **antigen presenting** cells are **dendritic** cells. The depletion is achieved by administration of immunosuppressant e.g. cyclosporine, desoxyspergualine, **rapamycin**, or FK506, and the re-population is induced by growth factor e.g. growth hormone, somatomedin, or insulin-like growth factor 1. The method was used for treating autoimmune diseases, for preventing graft-vs-host disease in allogenic bone marrow transplant, and for prolonging survival of skin allografts.

L3 ANSWER 40 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:229326 CAPLUS
DOCUMENT NUMBER: 126:258714
TITLE: Donor pretreatment with methylprednisolone synergistically prolongs survival of cardiac allografts in sensitized rat recipients conditioned with **rapamycin**
AUTHOR(S): Schmidbauer, G.; Homeyer, A.; Bohle, R. M.; Grimm, H.;
Binder, J.; Kupiec-Weglinski, J.W.
CORPORATE SOURCE: Department of Surgery, Justus-Liebig University, Giessen, Giessen, 35385, Germany
SOURCE: Transplantation Proceedings (1997), 29(1/2), 607-608
CODEN: TRPPA8; ISSN: 0041-1345

PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In rat heart allografts, pretreatment of the donor with methylprednisolone together with **rapamycin** treatment in the effector phase in sensitized rat recipients, abrogates accelerated rejection and synergistically prolongs cardiac allograft survival. This treatment decreased the transplant infiltration by host T-cytotoxic/suppressor and B-cells. This optimized methylprednisolone plus **rapamycin** treatment regimen increased cell proliferative immune responses to alloantigen, as detd. by mixed lymphocyte response, and decreased IgG and IgM responses in sensitized hosts. Such a striking therapeutic effect may result not only from the anticipated **rapamycin**-induced clonal anergy, but also from altered **antigen presentation** by the transplanted organ after conditioning of the donor with methylprednisolone.

L3 ANSWER 41 OF 49 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 97290381 MEDLINE
DOCUMENT NUMBER: 97290381 PubMed ID: 9145038
TITLE: Immunosuppressive agents in clinical trials in transplantation.
AUTHOR: Halloran P F
CORPORATE SOURCE: Division of Nephrology and Immunology, University of Alberta, Edmonton, Canada.. phil.halloran@ualberta.ca
SOURCE: AMERICAN JOURNAL OF THE MEDICAL SCIENCES, (1997 May) 313 (5) 283-8. Ref: 39
Journal code: 0370506. ISSN: 0002-9629.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970609
Last Updated on STN: 19970609
Entered Medline: 19970529
AB Many new agents are in or near clinical trials in organ transplantation. The small molecule antibioticlike drugs are inhibitors of key enzymes in T-cell signal transduction (calcineurin target of **rapamycin** [TOR], and inosine monophosphate dehydrogenase). Calcineurin inhibitors include cyclosporine microemulsion formulation generic cyclosporine preparations, and tacrolimus. **Rapamycin** (also known as **sirolimus**) acts on target of **rapamycin** to abrogate signals necessary for clonal expansion and is now in phase III. Recent trials of mycophenolate mofetil, an inhibitor of inosine monophosphate dehydrogenase, have shown that it reduces acute renal graft rejection when used with steroids and cyclosporine. New protein reagents in trials include polyclonal antilymphocyte antibodies, mouse monoclonal antibodies, "humanized" mouse monoclonals, and engineered proteins based on naturally occurring signalling molecules. Humanized antibodies against the interleukin-2 receptor are promising because humanized antibodies should combine low toxicity with the potential for long-term use. Engineered

human proteins designed to block costimulatory molecules on **antigen-presenting** cells could have similar potential for low toxicity and extended use. These agents are designed to reduce acute rejection and the toxicity of the existing drugs and eventually improve long-term patient and graft survival. Organ transplant practice will probably change considerably as these agents become available.

L3 ANSWER 42 OF 49 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 97130434 MEDLINE
DOCUMENT NUMBER: 97130434 PubMed ID: 8976197
TITLE: A role for endogenous transforming growth factor beta 1 in Langerhans cell biology: the skin of transforming growth factor beta 1 null mice is devoid of epidermal Langerhans cells.
AUTHOR: Borkowski T A; Letterio J J; Farr A G; Udey M C
CORPORATE SOURCE: Dermatology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892-1908, USA.
CONTRACT NUMBER: AG 04350 (NIA)
AI 24137 (NIAID)
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1996 Dec 1) 184 (6) 2417-22.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19990129
Entered Medline: 19970130

AB Transforming growth factor beta 1 (TGF-beta 1) regulates leukocytes and epithelial cells. To determine whether the pleiotropic effects of TGF-beta 1, a cytokine that is produced by both keratinocytes and Langerhans cells (LC), extend to epidermal leukocytes, we characterized LC (the epidermal contingent of the **dendritic** cell [DC] lineage) and **dendritic** epidermal T cells (DETC) in TGF-beta 1 null (TGF-beta 1 -/-) mice. I-A+ LC were not detected in epidermal cell suspensions or epidermal sheets prepared from TGF-beta 1 -/- mice, and epidermal cell suspensions were devoid of allostimulatory activity. In contrast, TCR-gamma delta + DETC were normal in number and appearance in TGF-beta 1 -/- mice and, importantly, DETC represented the only leukocytes in the epidermis. Immunolocalization studies revealed CD11c+ DC in lymph nodes from TGF-beta 1 -/- mice, although gp40+ DC were absent. Treatment of TGF-beta 1 -/- mice with **rapamycin** abrogated the characteristic inflammatory wasting syndrome and prolonged survival indefinitely, but did not result in population of the epidermis with LC. Thus, the LC abnormality in TGF-beta 1 -/- mice is not a consequence of inflammation in skin or other organs, and LC development is not simply delayed in these animals. We conclude that endogenous TGF-beta 1 is essential for normal murine LC development or epidermal localization.

L3 ANSWER 43 OF 49 MEDLINE
ACCESSION NUMBER: 96252073 MEDLINE
DOCUMENT NUMBER: 96252073 PubMed ID: 8680047
TITLE: Molecular mechanisms of new immunosuppressants.

AUTHOR: Halloran P F
CORPORATE SOURCE: Division of Nephrology and Immunology, University of Alberta Faculty of Medicine, Edmonton, Canada.
SOURCE: CLINICAL TRANSPLANTATION, (1996 Feb) 10 (1 Pt 2) 118-23.
Ref: 45
Journal code: 8710240. ISSN: 0902-0063.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 19960828
Last Updated on STN: 19990129
Entered Medline: 19960822

AB Maintenance immunosuppressive drugs act by partially blocking rate-limiting steps in the immune response. The new maintenance immunosuppressive drugs are either inhibitors of de novo synthesis of nucleotides (purines or pyrimidines), or are immunophilin-binding drugs that inhibit signal transduction in lymphocytes. The new inhibitors of de novo nucleotide synthesis include mycophenolate mofetil (MMF), mizoribine (MZ), brequinar (BQR), and leflunomide (LEF). MMF and MZ act to inhibit de novo purine synthesis, by inhibition of inosine monophosphate dehydrogenase (IMPDH). They create a selective immunodeficiency in T and B lymphocytes. MMF is hydrolyzed to mycophenolic acid (MPA), an uncompetitive inhibitor of IMPDH. MPA reduces the pools of guanine nucleotides, and increases some adenine nucleotides, inhibiting the cell cycle. Thus the number of specific effector T and B lymphocytes is reduced by limiting clonal expansion. MZ is a competitive inhibitor of IMPDH, which creates a similar defect. The relative clinical effectiveness of MMF versus MZ is not known. MMF has been approved in a number of countries; MZ has been approved in Japan. The inhibitors of de novo pyrimidine synthesis (BQR, LEF) act on the enzyme dehydroorotate dehydrogenase. Neither is currently in clinical trials in transplantation. The new immunophilin-binding drugs inhibit either the calcium-dependent phosphatase calcineurin (CN) [tacrolimus (or FK-506) and the microemulsion form of cyclosporine (CsA)] or signaling from growth factor receptors [**rapamycin (sirolimus)**]. Tacrolimus binds to FK binding protein-12 (FKBP-12) to create a complex that inhibits CN. CsA binds to cyclophilin to create a complex that inhibits CN. Inhibition of CN prevents activation of cytokine genes in T cells. The relative clinic effectiveness of tacrolimus versus microemulsion CsA is unknown. **Rapamycin** inhibits signaling from growth factor receptors, such as IL-2R. **Rapamycin** binds to FKBP to create a complex that engages proteins called TOR (target of **rapamycin**), or RAFT (**rapamycin** and FKBP target), which may be kinases. The result is a block in the ability of cytokine receptors to activate cell cycling, interfering with clonal expression. Deoxyspergualin, a parenteral drug in development for induction or antirejection therapy, may inhibit intracellular chaperoning by Hsc70, a member of the heat shock protein

family. It may have its principal effect by inhibiting the activation of transcription factor NF-kappa B in **antigen-presenting** cells and monocytes.

L3 ANSWER 44 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:321379 CAPLUS
DOCUMENT NUMBER: 120:321379
TITLE: Method for induction of antigen-specific immune tolerance
INVENTOR(S): Beschorner, William E.
PATENT ASSIGNEE(S): Johns Hopkins University School of Medicine, USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9405323	A1	19940317	WO 1992-US7620	19920904
W: CA				

PRIORITY APPLN. INFO.: WO 1992-US7620 19920904

AB Antigen-specific immune tolerance is induced by depletion of resident thymic **antigen presenting** cells (APCs) (e.g., with an immunosuppressive agent) and re-population of the thymus with new APCs contg. the antigen for tolerance. The recipient animal is further administered a thymic regeneration agent (e.g., a growth factor). Rat allogeneic skin grafts survived longer when 1st being treated with cyclosporine and then receiving **dendritic** cells from the skin graft donor strain along with recombinant human IGF-1. Both enhancement of thymic regeneration (with IGF-1) and **dendritic** cells were essential for prolongation of the skin graft survival.

L3 ANSWER 45 OF 49 MEDLINE
ACCESSION NUMBER: 94303963 MEDLINE
DOCUMENT NUMBER: 94303963 PubMed ID: 7518204
TITLE: The effect of immunosuppressants on human leukocyte NADPH oxidase.
AUTHOR: Engelbrecht M E; Oosthuizen M M; Myburgh J A
CORPORATE SOURCE: Department of Surgery, University of the Witwatersrand Medical School, Johannesburg, South Africa.
SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1994 Jun 17) 723 436-8.
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940818
Last Updated on STN: 19990129
Entered Medline: 19940805

L3 ANSWER 46 OF 49 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 94323890 MEDLINE
DOCUMENT NUMBER: 94323890 PubMed ID: 8047990
TITLE: Prolonged survival without posttransplant immunosuppression

in a large animal model.

AUTHOR: Granger D K; Matas A J; Jenkins M K; Moss A A; Chen S C; Almond P S
CORPORATE SOURCE: Department of Surgery, University of Minnesota, Minneapolis.
CONTRACT NUMBER: DK07566 (NIDDK)
SOURCE: SURGERY, (1994 Aug) 116 (2) 236-41.
Journal code: 0417347. ISSN: 0039-6060.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940909
Last Updated on STN: 19990129
Entered Medline: 19940830

AB BACKGROUND. T cells that receive T-cell antigen receptor signals but do not undergo mitosis become unresponsive to subsequent antigenic stimulation. This can be achieved by **antigen presentation** to T cells in the absence of critical costimulatory signals from **antigen-presenting** cells (APC) or in the presence of the antiproliferative drug **rapamycin**. In mice, peritransplant infusion of adherent APC-depleted splenocytes, which do not provide costimulatory signals to T cells in vitro, leads to T-cell unresponsiveness in vivo and specifically prolongs the survival of skin grafts that express the major histocompatibility complex (MHC) molecules expressed by the transfused cells. Our goal was to determine whether in vivo infusion of adherent APC-depleted donor peripheral blood mononuclear cells (PBMC), with or without **rapamycin**, induces prolonged kidney allograft survival in a large animal model. METHODS. MHC homozygous inbred miniature swine (SLAcc) were transfused with **dendritic** cell-monocyte-depleted (G10-passed) PBMC (2.5 x 10(8) cells) from MHC disparate SLAdd donors, with and without three peritransfusion infections of **rapamycin** (0.25 mg/kg/day intramuscularly) the day before, the day of, and the day after the transfusion. SLAcc recipients received an SLAdd kidney transplant 6 days later. No posttransplant immunosuppression was given. RESULTS. In contrast to donor-specific whole blood transfusions, which uniformly resulted in sensitization and hyperacute rejection (less than 1 day), renal allograft survival in animals that received a transfusion of G10-passed PBMC from their eventual kidney donor was similar (mean, 8.1 +/- 4.5 days) to untreated controls (mean, 7.8 +/- 5.0 days). Pretransplant **rapamycin** alone also had no effect on survival (mean, 7.7 +/- 8.1 days) versus controls. The combination of G10-passed blood and peritransfusion **rapamycin**, however, increased survival significantly (mean, 27.3 +/- 10.4 days) ($p = 0.01$ versus untreated recipients or recipients of only G10-passed PBMC; $p = 0.03$ versus recipients of **rapamycin** alone). CONCLUSIONS. Pretransplant transfusion with costimulator-deficient donor PBMC plus peritransfusion **rapamycin** treatment, but neither alone, prolongs renal allograft survival in pigs without posttransplant immunosuppression. This strategy, once optimized, may be applicable to human transplant tolerance.

L3 ANSWER 47 OF 49 MEDLINE DUPLICATE 20

ACCESSION NUMBER: 94373841 MEDLINE
DOCUMENT NUMBER: 94373841 PubMed ID: 7522130
TITLE: FK506 and cyclosporin A each inhibit antigen-specific signaling in the T cell line 171 in the absence of a calcium signal.
AUTHOR: Metcalfe S; Alexander D; Turner J
CORPORATE SOURCE: Department of Surgery, University of Cambridge, United Kingdom.
SOURCE: CELLULAR IMMUNOLOGY, (1994 Oct 1) 158 (1) 46-58.
Journal code: 1246405. ISSN: 0008-8749.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199410
ENTRY DATE: Entered STN: 19941031
Last Updated on STN: 19980206
Entered Medline: 19941020

AB Antigen-specific signal transduction leading to IL2 induction and secretion in the T cell line 171 is augmented by association of p56lck with CD4. Although no change in cytoplasmic calcium level ([Ca2+]i) was detectable during antigen-specific signal transduction of 171-CD4+ cells, IL2 induction was inhibited by FK506 and CsA. Since these drugs are thought to act selectively by inhibiting calcineurin, a calcium-calmodulin-dependent protein phosphatase associated with activation of the IL2 promoter, we considered the possibility that calcineurin is constitutively active in 171 cells. However, we found no evidence for this because PMA failed to supplement any putatively active calcineurin to induce IL2 secretion. We suggest that IL2 secretion induced by **antigen presentation** to TCR/CD4/p56lck requires an FK506 and cyclosporin A-sensitive step which may be independent of calcium signaling. **Rapamycin** did not inhibit IL2 secretion induced by TCR/CD4/p56lck, emphasizing the specific action of FK506 and cyclosporin A.

L3 ANSWER 48 OF 49 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 94037636 MEDLINE
DOCUMENT NUMBER: 94037636 PubMed ID: 8222329
TITLE: Anti-CD28 antibody- and IL-4-induced human T cell proliferation is sensitive to **rapamycin**.
AUTHOR: Luo H; Chen H; Daloze P; St-Louis G; Wu J
CORPORATE SOURCE: Laboratory of Nephrology and Transplantation Immunology, Notre-Dame Hospital Research Centre, Montreal, Quebec, Canada.
SOURCE: CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (1993 Nov) 94 (2) 371-6.
Journal code: 0057202. ISSN: 0009-9104.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19990129
Entered Medline: 19931214

AB **Rapamycin** (RAPA) is a potent immunosuppressant. In this study we

investigated the effect of RAPA on T cell proliferation triggered by various stimuli in an in vitro human model. The proliferation of T cells stimulated via an alternative pathway using phorbol myristate acetate (PMA) and anti-CD28 antibody (alpha CD28) in the absence of **antigen-presenting** cells (APC) was strongly inhibited by RAPA. T cell proliferation provoked via a combination of CD3/TCR and CD28 pathways using anti-CD3 antibody (alpha CD3) plus alpha CD28 was also inhibited by RAPA in the presence of APC. The mitogen (phytohaemagglutinin (PHA) or alpha CD3)-induced up-regulation of expression of the IL-2 receptor alpha chain (IL-2R alpha) and the IL-4 receptor (IL-4R) was sensitive to RAPA. This suggests that RAPA's interference with the IL-2 and IL-4 autocrine loops during T cell activation might contribute to RAPA's overall immunosuppressive effect. We have further demonstrated in a two-stage culture system that RAPA strongly inhibited IL-4-stimulated proliferation of T cells, the latter being either pretreated with alpha CD3 in the presence of APC, or with PMA plus alpha CD28 in the absence of APC. The result suggests that the Ca++ influx during the pretreatment is not obligatory for T cells to achieve IL-4 responsiveness. The results also indicate that RAPA's antiproliferative effect on IL-4-stimulated T cells is not contingent on the various mechanisms of cell priming. Therefore, RAPA's major target is probably at the second stage after the priming. Our study has extended current knowledge about the effect of RAPA on human T cells.

L3 ANSWER 49 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:75908 CAPLUS
DOCUMENT NUMBER: 116:75908
TITLE: Evaluation of the influence of FK 506, **rapamycin**, and cyclosporine on processing and presentation of particulate antigen by macrophages: assessment of a drug "carry-over" effect
AUTHOR(S): Cooper, Mark H.; Gregory, S. H.; Thomson, A. W.; Fung, J. J.; Starzl, T. E.; Wing, E. J.
CORPORATE SOURCE: Sch. Med., Univ. Pittsburgh, Pittsburgh, PA, 15232, USA
SOURCE: Transplantation Proceedings (1991), 23(6), 2957-8
CODEN: TRPPA8; ISSN: 0041-1345
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The incubation of HKLM and 5A9 T cells with drug-pretreated macrophages resulted in significant suppression of antigen-induced T-cell proliferation. This suppression occurred regardless of whether macrophages were treated with FK 506, CyA, or **rapamycin**. The nonspecific proliferation of splenocytes to ConA was also inhibited in cocultures contg. drug-treated macrophages indicating our inability to wash drug from out of our system. Results confirm previous studies by others in which a significant suppression of the T-cell response to antigen was obsd. when the cells were cocultured with macrophages pretreated with CyA. These latter studies however, gave little credence to the possibility of drug carry over.

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L22 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:744583 CAPLUS
DOCUMENT NUMBER: 130:137891
TITLE: Resurrecting the dead: DCs cross-present antigen derived from apoptotic cells on MHC I
AUTHOR(S): Albert, Matthew L.; Bhardwaj, Nina
CORPORATE SOURCE: Rockefeller University, New York, NY, 10021-6399, USA
SOURCE: Immunologist (**1998**), 6(5), 194-198
CODEN: INOLEG; ISSN: 1192-5612
PUBLISHER: Hogrefe & Huber Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 45 refs. discussing phagocytosis of apoptotic cells by immature dendritic cells and generation of MHC class I/peptide complexes, and tolerance of T-cells by dendritic cells.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L22 ANSWER 11 OF 13 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998438585 MEDLINE
DOCUMENT NUMBER: 98438585 PubMed ID: 9763615
TITLE: Immature **dendritic** cells **phagocytose** **apoptotic** cells via alphavbeta5 and CD36, and cross-present antigens to cytotoxic T lymphocytes.
AUTHOR: Albert M L; Pearce S F; Francisco L M; Sauter B; Roy P; Silverstein R L; Bhardwaj N
CORPORATE SOURCE: Laboratory of Cellular Physiology and Immunology, The Rockefeller University, New York 10021, USA.
CONTRACT NUMBER: EY-10967 (NEI)
GM-07793 (NIGMS)
HL-42540 (NHLBI)
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, **(1998 Oct 5)** 188 (7) 1359-68.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990106
Last Updated on STN: 19990106
Entered Medline: 19981116

AB Dendritic cells, but not macrophages, efficiently phagocytose apoptotic cells and cross-present viral, tumor, and self-antigens to CD8(+) T cells.

This in vitro pathway corresponds to the in vivo phenomena of cross-priming and cross-tolerance. Here, we demonstrate that phagocytosis of apoptotic cells is restricted to the immature stage of dendritic cell (DC) development, and that this process is accompanied by the expression of a unique profile of receptors, in particular the alphavbeta5 integrin and CD36. Upon maturation, these receptors and, in turn, the phagocytic capacity of DCs, are downmodulated. Macrophages engulf apoptotic cells more efficiently than DCs, and although they express many receptors that mediate this uptake, they lack the alphavbeta5 integrin. Furthermore, in contrast to DCs, macrophages fail to cross-present antigenic material contained within the engulfed apoptotic cells. Thus, DCs use unique pathways for the phagocytosis, processing, and presentation of antigen derived from apoptotic cells on class I major histocompatibility complex. We suggest that the alphavbeta5 integrin plays a critical role in the trafficking of exogenous antigen by immature DCs in this cross-priming pathway.

L22 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:83080 BIOSIS

DOCUMENT NUMBER: PREV200100083080

TITLE: **Dendritic** cells **phagocytose** **apoptotic** melanoma cells and induce cytolytic and proliferative T cell responses.

AUTHOR(S): Muthana, M. (1); Sisley, K.; Rennie, I.; Murray, A. K. (1)

CORPORATE SOURCE: (1) Division of Oncology and Cellular Pathology, University of Sheffield, Beech Hill Rd, Sheffield, S102RX UK

SOURCE: Immunology, (**December**, **2000**) Vol. 101, No. Supplement 1, pp. 98. print.
Meeting Info.: Annual Congress of the British Society for Immunology Harrogate, UK December 05-08, 2000 British Society for Immunology
. ISSN: 0019-2805.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

L22 ANSWER 6 OF 13 MEDLINE DUPLICATE 3

ACCESSION NUMBER: 2000426004 MEDLINE
DOCUMENT NUMBER: 20424192 PubMed ID: 10969791
TITLE: Dendritic cells containing apoptotic melanoma cells prime human CD8+ T cells for efficient tumor cell lysis.
AUTHOR: Jenne L; Arrighi J F; Jonuleit H; Saurat J H; Hauser C
CORPORATE SOURCE: Department of Dermatology, University Hospital Geneva, Switzerland.
SOURCE: CANCER RESEARCH, **(2000 Aug 15)** 60 (16) 4446-52.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000922
Last Updated on STN: 20000922
Entered Medline: 20000914

AB **Dendritic** cells (DCs) **phagocytose apoptotic** influenza-infected monocytes and cross-present influenza antigen to CD8+ T cells, generating a specific CTL response. We investigated whether apoptotic melanoma cells, presented by this mechanism, can lead to CTL responses to tumor-associated antigens and melanoma cells. Apoptotic HLA-A2- MEL-397 melanoma cells were internalized by HLA-A2+ immature monocyte-derived DCs but failed to induce maturation of DCs. When exposed to interleukin 6, interleukin 1beta, tumor necrosis factor alpha, and prostaglandin E2, DCs containing apoptotic MEL-397 cell material matured normally [cross-presenting DCs (cp-DCs)]. Autologous CD8+ CTL lines generated with cp-DCs produced tumor necrosis factor when stimulated with HLA-A2-binding immunodominant peptides from MelanA/MART1 and MAGE-3 (expressed by MEL-397 cells) but not tyrosinase (absent in MEL-397). T2 target cells loaded with the respective peptides were lysed by these cell lines, although to a lesser extent than by CTL lines generated in the presence of mature DCs and peptides from melanoma-associated h antigens. In contrast, lines generated with cp-DCs lysed HLA-A2+ MEL-526 melanoma cells or allogenic HLA-A2+ cp-DCs efficiently, whereas the CTL generated with DCs and peptides had little lytic activity. Mature DCs containing apoptotic tumor cells may thus represent an alternative approach for the therapy of malignant tumors.

L26 ANSWER 1 OF 1 LIFESCI COPYRIGHT 2003 CSA
ACCESSION NUMBER: 95:47470 LIFESCI
TITLE: The value of epitope mapping in autoimmune diseases
AUTHOR: Carson, D.A.
CORPORATE SOURCE: Dep. Med., Univ. California, San Diego, CA 92093, USA
SOURCE: J. CLIN. INVEST., (**1994**) vol. 94, no. 5, p 1713.
ISSN: 0021-9738.
DOCUMENT TYPE: Journal
TREATMENT CODE: General Review
FILE SEGMENT: F
LANGUAGE: English

AB Autoantibody synthesis accompanies many idiopathic chronic inflammatory diseases. Autoantibody assays are useful diagnostic tools. However, autoantibodies against intracellular components cannot cause the destruction of an intact cell under normal conditions. Epitope mapping of recombinant proteins has defined the principal antigenic determinants that are recognized by various autoantibodies. One aim of these studies has been to identify regions of autoantigens that might cross react antigenically with environmental pathogens. However, the results have been inconclusive, because most antibodies recognize complex three-dimensional structures that depend upon protein folding. It has proven very difficult to pinpoint a particular amino acid sequence that constitutes an entire autoantibody epitope. T lymphocytes, as opposed to antibodies, recognize short linear peptides bound to class I or class II major histocompatibility complex (MHC) molecules. Interstitial tissue macrophages and **dendritic** cells, that **ingest** **apoptotic** cells, may have access to peptides derived from sequestered cytosolic antigens. A few hundred peptide molecules loaded on MHC antigens of dendritic cells can activate antigen-specific T helper cells. Cytokines released from activated T lymphoblasts may cause damage to adjacent normal cells, and can help B lymphocytes to proliferate and differentiate into plasma cells. Hence, recent epitope mapping studies of self-antigens have focused on autoreactive T lymphocytes, rather than autoantibodies.

L34 ANSWER 13 OF 13 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 95123101 MEDLINE
DOCUMENT NUMBER: 95123101 PubMed ID: 7529805
TITLE: Role of B7:CD28/CTLA-4 in the induction of chronic relapsing experimental allergic encephalomyelitis.
AUTHOR: Perrin P J; Scott D; Quigley L; **Albert P S**; Feder O; Gray G S; Abe R; June C H; Racke M K
CORPORATE SOURCE: Immune Cell Biology Program, Naval Medical Research Institute, Bethesda, MD 20889.
SOURCE: JOURNAL OF IMMUNOLOGY, (1995 Feb 1) 154 (3) 1481-90. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950223
Last Updated on STN: 20000303
Entered Medline: 19950216

AB T cell activation requires both Ag/MHC recognition and costimulatory signals. The present studies were designed to test whether the loss of **tolerance** to myelin basic protein (MBP) requires costimulation by members of the B7 receptor family. CTLA-4Ig, a fusion protein ligand for B7-1 and B7-2, was used to assess the role of B7-mediated costimulation in chronic relapsing experimental allergic encephalomyelitis (EAE) induced by the transfer of MBP specific T cell lines. In adoptively transferred EAE, administering CTLA-4Ig to donor mice or during in vitro activation of MBP specific-T cells resulted in diminution of clinical disease. The presence of CTLA-4Ig during both the immunization and in vitro activation stages was most effective in preventing clinical signs of disease. This diminution in clinical disease was paralleled by a decreased proliferative response and reduced production of IL-2 and IL-4, but not IFN-gamma, after antigenic stimulation of encephalitogenic T cells in vitro. In contrast, CTLA-4Ig treatment of recipient animals after the transfer of MBP-activated T cells affected neither disease course nor severity. These results indicate that additional costimulatory pathways may be involved in established EAE, or that some cells are independent of costimulation or, alternatively, that CTLA-4Ig does not enter brain parenchyma in therapeutic concentrations. Thus, we conclude that costimulation provided by B7 molecules plays a major role in the development of encephalitogenic T cells and in the establishment of chronic relapsing EAE, a prototypic **CD4**+ T cell-mediated autoimmune disease.

L34 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:187442 CAPLUS
DOCUMENT NUMBER: 128:307488
TITLE: Dendritic cells acquire antigen from apoptotic cells and induce class I-restricted CTLs
AUTHOR(S): **Albert, Matthew L.**; Sauter, Birthe; Bhardwaj, Nina
CORPORATE SOURCE: Lab. Cellular Physiology and Immunology, Rockefeller Univ., New York, NY, 10021, USA
SOURCE: Nature (London) (1998), 392(6671), 86-89
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Macmillan Magazines
DOCUMENT TYPE: Journal
LANGUAGE: English

AB CD8+ cytotoxic T lymphocytes (CTLs) mediate resistance to infectious agents and tumors. Classically, CTLs recognize antigens that are localized in the cytoplasm of target cells, processed and presented as peptide complexes with class I mols. of the major histocompatibility complex (MHC). However, there is evidence for an exogenous pathway whereby antigens that are not expected to gain access to the cytoplasm are presented on MHC class I mols. The most dramatic example is the in vivo phenomenon of cross-priming: antigens from donor cells are acquired by bone marrow-derived host antigen-presenting cells (APCs) and presented on MHC class I mols. Two unanswered questions concern the identity of this bone marrow-derived cell and how such antigens are acquired. Here the authors show that human dendritic cells, but not macrophages, efficiently present antigen derived from apoptotic cells, stimulating class I-restricted CD8+ CTLs. The authors' findings suggest a mechanism by which potent APCs acquire antigens from tumors, transplants, infected cells, or even self-tissue, for stimulation or tolerization of CTLs.

L3 ANSWER 36 OF 49 MEDLINE DUPLICATE 15

ACCESSION NUMBER: 1998406344 MEDLINE
DOCUMENT NUMBER: 98406344 PubMed ID: 9733606
TITLE: Flow cytometric analysis of chimerism in the rat tolerant to a renal allograft.
AUTHOR: Naar J D; Fisher R A; Saggi B H; Wakely P E Jr; Tawes J W; Posner M P
CORPORATE SOURCE: Division of Transplant Surgery, Medical College of Virginia/Virginia Commonwealth University, Richmond, Virginia, 23298-0254, USA.
SOURCE: JOURNAL OF SURGICAL RESEARCH, (1998 Jul 1) 77 (2) 179-86.

Journal code: 0376340. ISSN: 0022-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19981006
Last Updated on STN: 19990129
Entered Medline: 19980924

AB BACKGROUND: Chimerism, produced by the two-way migration of cells between graft and host, is a proposed mechanism by which tolerance occurs. The appearance of donor/recipient chimeras in tolerant ACI to Lewis rat heterotopic renal transplants was assessed in peripheral blood leukocytes using flow cytometry after staining with monoclonal antibodies. MATERIALS AND METHODS: ACI and Lewis rats were used as donor and recipient, respectively, after **Rapamycin** and Cyclosporin immunosuppression with or without donor blood or bone marrow transfusion. ACI and Lewis animals were also used for isograft and single-kidney controls. Animals were sacrificed at various time points after initial operation. Flow cytometry was performed on isolated peripheral blood leukocytes at sacrifice. Histologic and functional data were also obtained. The monoclonal antibody panel included RT1(a) (ACI, MHC I) combined with CD2, CD4, CD8, CD16, and CD25 or RT1(a,c) (bone marrow chimeras). RESULTS: RT1(a)+, CD8+ cells were transiently present in the peripheral blood leukocytes of Lewis recipients with the exception of allogeneic bone marrow recipients. No significant number of RT1(a)+, CD16+ ("**dendritic**" cell-line) chimeras was seen. Veto cells (RT1(a,c)+) were transiently present in the bone marrow recipients, but they did not lead to improved outcome. Furthermore, no correlation was made between histologic tolerance and any of these donor-derived cells. CONCLUSION: Donor/recipient chimerism, and the veto cell phenomenon are not operational tolerance mechanisms in this stringent model of ACI to Lewis rat renal transplantation.

L3 ANSWER 34 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1999:510797 BIOSIS

DOCUMENT NUMBER: PREV199900510797

TITLE: Specific effects of corticosteroids on the differentiation and maturation of human **dendritic** cells.

AUTHOR(S): Woltman, Andrea M. (1); Kamerling, Sylvia W. A. (1); Daha, Mohamed R. (1); de Fijter, Hans W. (1); van Kooten, Cees (1)

CORPORATE SOURCE: (1) Nephrology, Leiden University Medical Center, Leiden Netherlands

SOURCE: Journal of the American Society of Nephrology, (Sept., 1999) Vol. 10, No. PROGRAM AND ABSTR. ISSUE, pp. 717A. Meeting Info.: 32nd Annual Meeting of the American Society of Nephrology Miami Beach, Florida, USA November 1-8, 1999 American Society of Nephrology . ISSN: 1046-6673.

DOCUMENT TYPE: Conference

LANGUAGE: English

L3 ANSWER 33 OF 49 MEDLINE DUPLICATE 14

ACCESSION NUMBER: 1999455500 MEDLINE
DOCUMENT NUMBER: 99455500 PubMed ID: 10526580
TITLE: Dexamethasone enhances CTLA-4 expression during T cell activation.
AUTHOR: Xia M; Gasser J; Feige U
CORPORATE SOURCE: Department of Pharmacology, Amgen Inc., Thousand Oaks, California 91329-1789, USA.
SOURCE: CELLULAR AND MOLECULAR LIFE SCIENCES, (1999 Sep) 55 (12) 1649-56.
Journal code: 9705402. ISSN: 1420-682X.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991102

AB T cell activation is enhanced by the costimulatory interaction of B7 on **antigen-presenting** cells and CD28 on T cells, resulting in long-term T cell proliferation, differentiation and production of large amounts of cytokines, such as interleukin (IL)-2. CTLA-4 is a co-stimulation receptor that shares 31% homology with CD28 and binds B7 family members with higher affinity. CTLA-4 is transiently expressed intracellularly and on the cell surface following activation of T cells. We have studied the kinetics of CTLA-4 expression and the effects of dexamethasone on CTLA-4 expression during T cell activation in cultures of mouse spleen cells stimulated by a mixture of immobilized anti-CD3 and anti-CD28 monoclonal antibodies (anti-CD3/CD28 mAb) or concanavalin A (ConA). CTLA-4 expression peaked on day 2 and returned to background levels after 7 days. Dexamethasone was found to potentiate CTLA-4 expression in a dose-dependent manner with an EC50 effective concentration 50%) of about 10(-8) M. In contrast, other immunosuppressive agents, such as **rapamycin** or cyclosporin A had no or an inhibitory effect on CTLA-4 expression, respectively. Dexamethasone also stimulated CD28 expression, but inhibited IL-2R expression during anti-CD3/CD28 mAb-induced mouse splenic T cell activation. Western blot analyses of lysates of activated mouse T cells showed that dexamethasone increased CTLA-4 protein levels twofold during anti-CD3/CD28 mAb-induced activation.

Dexamethasone also enhanced CTLA-4 messenger RNA twofold as quantified by ribonuclease protection assay. The effects of dexamethasone on CTLA-4 expression were glucocorticoid-specific and completely inhibited by the glucocorticoid receptor antagonist mifepristone (RU486), indicating that the effect of dexamethasone on CTLA-4 expression is mediated through the glucocorticoid receptor. In conclusion, the immunosuppressive agent dexamethasone actually stimulates CTLA-4 expression, which is involved in downregulation of T cell activation.

L3 ANSWER 32 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:783950 CAPLUS
DOCUMENT NUMBER: 132:9021
TITLE: Methods and agents for modulating the immune response and inflammation involving monocyte and **dendritic** cell membrane proteins
INVENTOR(S): Beaulieu, Sylvie; Randolph, Gwendalyn J.; Muller, William A.; Steinman, Ralph M.
PATENT ASSIGNEE(S): The Rockefeller University, USA; The Cornell Research Foundation
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9962537	A1	19991209	WO 1999-US12681	19990604
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9944237	A1	19991220	AU 1999-44237	19990604
PRIORITY APPLN. INFO.:			US 1998-90781	19980604
			WO 1999-US12681	19990604

AB Methods and agents are provided to decrease or increase the migration of **dendritic** cells for the suppression or enhancement, resp., of the development of immunity and the immune response, by modulating the **dendritic** cell membrane proteins p-glycoprotein (MDR-1) and tissue factor. Agents which suppress migration have utility in the treatment of immunol.-mediated and inflammatory diseases, e.g. graft rejection, contact dermatitis, seasonal allergies, asthma, and food allergies. Agents which enhance migration are useful for increasing the effectiveness of vaccines.

Agents are also disclosed which enhance the migration of monocytes, useful in the treatment of chronic inflammatory diseases. Methods are also provided for identifying useful agents by measuring the effect on **dendritic** cell migration of agents which modulate p-glycoprotein and tissue factor activity, as well as the effect of agents on monocyte migration.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 31 OF 49 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 2000208644 MEDLINE
DOCUMENT NUMBER: 20208644 PubMed ID: 10746855
TITLE: Immunosuppressive agents in organ transplantation: past, present, and future.
AUTHOR: Hong J C; Kahan B D
CORPORATE SOURCE: Department of Surgery, The University of Texas Medical School at Houston, 77030, USA.
SOURCE: SEMINARS IN NEPHROLOGY, (2000 Mar) 20 (2) 108-25. Ref: 174
Journal code: 8110298. ISSN: 0270-9295.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000512
Last Updated on STN: 20000512
Entered Medline: 20000428

AB The development of immunosuppressive agents reflects the progress in understanding the cellular and molecular mechanisms which mediate allograft rejection. Six paradigms represent the evolution of immunosuppressive strategies for organ transplantation. The proliferation paradigm advances agents which interrupt lymphocyte cell division (azathioprine, cyclophosphamide, mycophenolic acid). The depletion paradigm conscripts drugs that bind to lymphocyte cell surface markers, thereby producing cell lysis and/or inactivation (polyclonal ATGAM and thymoglobulin, and monoclonal OKT3 antilymphocyte antibodies). The cytokine paradigm uses agents that interrupt lymphocyte maturational events; eg, synthesis (calcineurin inhibitors: cyclosporine/tacrolimus), binding to surface receptors (anti-CD25 mAbs), or signal transduction phases of cytokine stimulation (**sirolimus**). The introduction of calcineurin inhibitors markedly reduces the rate of acute rejection episodes and increases short-term graft survival rates; nephrotoxicity and chronic allograft attrition remain as unanswered challenges. The cyclosporine A (CsA) sparing property of **sirolimus** permits the use of lower exposure to calcineurin agents, allows for early withdrawal of steroid therapy, and may delay allograft senescence. Furthermore, the combination of SRL with anti-IL-2R mAbs proffers an induction approach which allows prolonged periods of holiday from calcineurin inhibitors. To address the tissue nonselectivity of the calcineurin and mTOR inhibitors, which presumably causes the drug toxicities, new agents are being developed to selectively inhibit the T cell target Janus Kinase 3. In the costimulation paradigm, the accessory signals generated by **antigen -presenting** cells are interrupted by distinct agents: the receptor conjugate CTLA4-immunoglobulin and anti-B7 or anti-CD40 ligand mAbs. Another set of drugs (selectin blocking agents, anti-ICAM-1 antisense deoxy oligonucleotides, and the lymphocyte homing inhibitor FTY720) seeks to modulate the ischemia-reperfusion injury, which exacerbates cytokine-mediated events in the donor and the subsequent procurement injury and may also accelerate the progression of transplant senescence. Finally, the transplantation tolerance paradigm is based on the development of strategies which distort alloimmune recognition by antigen reactive cells (MHC peptides or proteins), produce anergy (costimulation blockers), functional inactivation, or deletion of

antigen-reactive cells (donor bone marrow infusions and gene therapy). Presently, the optimal immunosuppressive strategy uses combinations of agents that act in synergistic fashion to provide the potency, freedom from toxic reactions, convenience of administration, and cost appropriate for the individual patient.

L3 ANSWER 29 OF 49 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:205082 BIOSIS
DOCUMENT NUMBER: PREV200100205082
TITLE: The immunosuppressive drug **rapamycin** induces apoptosis in monocyte- and CD34-derived **dendritic** cells, but not in monocytes and macrophages.
AUTHOR(S): Woltman, A. M. (1); de Fijter, J. W. (1); Kamerling, S. W. A. (1); van der Kooij, S. W. (1); Paul, L. C. (1); Daha, M.
R. (1); van Kooten, C. (1)
CORPORATE SOURCE: (1) Department of Nephrology, Leiden University Medical Center, Leiden Netherlands
SOURCE: Immunobiology, (November, 2000) Vol. 203, No. 1-2, pp. 258-259. print.
Meeting Info.: Joint Annual Meeting of the German and Dutch
Societies of Immunology Duseldorf, Germany November 29-December 02, 2000
ISSN: 0171-2985.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L3 ANSWER 28 OF 49 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 2000289046 MEDLINE
DOCUMENT NUMBER: 20289046 PubMed ID: 10830234
TITLE: Analogs of 1,25-dihydroxyvitamin D3 as dose-reducing agents for classical immunosuppressants.
AUTHOR: van Etten E; Branisteanu D D; Verstuyf A; Waer M; Bouillon R; Mathieu C
CORPORATE SOURCE: Laboratory for Experimental Medicine and Endocrinology (LEGENDO), Katholieke Universiteit Leuven, Belgium.
SOURCE: TRANSPLANTATION, (2000 May 15) 69 (9) 1932-42.
Journal code: 0132144. ISSN: 0041-1337.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000616
Last Updated on STN: 20000616
Entered Medline: 20000608

AB BACKGROUND: Most immunosuppressants have a narrow margin between efficacy and side effects. A major goal in the development of immunomodulatory strategies is the discovery of combinations of drugs exerting synergistic immunomodulatory effects. The active form of vitamin D, 1,25(OH)2D3, is an immunomodulator that interacts with T cells but mainly targets **antigen-presenting** cells. We have demonstrated synergism between 1,25(OH)2D3 and cyclosporine, **rapamycin**, and FK506. The aim of this study was to investigate whether this synergism could be observed with other immunosuppressants (mycophenolate mofetil, leflunomide, and the methylxanthine A802715) and whether analogs of 1,25(OH)2D3 share this synergistic capacity in vivo. METHODS: In vitro, the median effect analysis was applied to the inhibition of phytohemagglutinin A-induced lymphocyte proliferation. In vivo, synergism between analogs of 1,25(OH)2D3 and cyclosporine or mycophenolate mofetil was evaluated in experimental autoimmune encephalomyelitis. RESULTS: In vitro, all combinations with 1,25(OH)2D3 were synergistic. The strongest synergism was seen with the inhibitors of interleukin 2 secretion, cyclosporine and FK506 (indexes 0.16 and 0.27, respectively). The weakest synergism was observed in combinations using A802715, a second-signal inhibitor (index 0.52), or the nucleotide synthesis inhibitor mycophenolate mofetil (index 0.43). In vivo, analogs of 1,25(OH)2D3 share the in vitro-observed synergism with 1,25(OH)2D3. Moreover, the differences in synergism with different immunomodulators were also present in vivo, where the best synergism was again seen in combination with cyclosporine (up to 100% paralysis protection). CONCLUSIONS: These data confirm that 1,25(OH)2D3 and its analogs are potent dose-reducing drugs for other immunomodulators, making them potentially interesting for clinical use in autoimmunity and transplantation.

L3 ANSWER 27 OF 49 MEDLINE DUPLICATE 11

ACCESSION NUMBER: 2001125734 MEDLINE
DOCUMENT NUMBER: 21064725 PubMed ID: 11133833
TITLE: Counter-regulation of cytolytic activity and cytokine production in HIV-1-specific murine CD8+ cytotoxic T lymphocytes by free antigenic peptide.
AUTHOR: Takahashi M; Nakagawa Y; Berzofsky J A; Takahashi H
CORPORATE SOURCE: Department of Microbiology and Immunology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8602, Japan.
SOURCE: INTERNATIONAL IMMUNOLOGY, (2001 Jan) 13 (1) 43-51. Journal code: 8916182. ISSN: 0953-8178.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010222

AB We have reported previously that the cytolytic activity of murine CD8(+) cytotoxic T lymphocytes (CTL) specific for HIV-1 gp160 envelope glycoprotein was markedly inhibited by brief exposure to the free minimal antigenic peptide (I-10: 10mer peptide from gp160) by direct binding to class I MHC molecules of specific CTL in the absence of **antigen-presenting** cells (APC). Here, we show that treatment of such CTL with the peptide induced not only the inhibition of cytolytic activity but also IL-2Rbeta down-modulation, followed by the inhibition of IL-2-dependent growth. The peptide-mediated inhibition and restoration of expression of IL-2Rbeta were well correlated with changes in both cytolytic activity and IL-2-dependent growth of the CTL. Since enzymatic activity of granzyme B, and mRNA expression of granzyme B and perforin were significantly reduced in peptide-treated CTL, the inhibition of cytolytic activity was mainly caused by the exhaustion of cytolytic molecules. Moreover, treatment of the CTL with the epitopic peptide resulted in production of high levels of IL-2, IFN-gamma, tumor necrosis factor-alpha and MIP-1beta in the culture supernatant. Maximum amounts of cytokines were obtained in the culture supernatant when the level of cytolytic activity was the lowest. Thus, although the CTL temporarily lost their cytolytic activities, they simultaneously gained the abilities to produce cytokines for activation of various cell populations. These changes induced by free antigenic peptide in CD8(+) CTL reveal an interesting counter-regulation between their cytolytic activities and cytokine production.

3 ANSWER 26 OF 49 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 2001357472 MEDLINE
DOCUMENT NUMBER: 21311408 PubMed ID: 11418477
TITLE: **Rapamycin** induces apoptosis in monocyte- and CD34-derived **dendritic** cells but not in monocytes and macrophages.
AUTHOR: Woltman A M; de Fijter J W; Kamerling S W; van Der Kooij S W; Paul L C; Daha M R; van Kooten C
CORPORATE SOURCE: Department of Nephrology, Leiden University Medical Center,
The Netherlands.
SOURCE: BLOOD, (2001 Jul 1) 98 (1) 174-80.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010730
Last Updated on STN: 20010730
Entered Medline: 20010726

AB **Rapamycin** (Rapa), a recently introduced immunosuppressive drug, seems to be effective in preventing acute allograft rejection. Although its antiproliferative effect on T lymphocytes has been investigated extensively, its effect on the initiators of the immune response, the **dendritic** cells (DCs), is not known. Therefore, the effect of Rapa on monocyte- (mo-DCs) and CD34(+)-derived DCs in vitro but also on other myeloid cell types, including monocytes and macrophages, was examined. The present study shows that Rapa does not affect phenotypic differentiation and CD40L-induced maturation of mo-DCs. However, Rapa dramatically reduced cell recovery (40%-50%). Relatively low concentrations of Rapa (10(-9) M) induced apoptosis in both mo-DCs and CD34(+)-derived DCs, as visualized by phosphatidylserine exposure, nuclear condensation and fragmentation, and DNA degradation. In contrast, Rapa did not affect freshly isolated monocytes, macrophages, or myeloid cell lines. The sensitivity to Rapa-induced apoptosis was acquired from day 2 onward of mo-DC differentiation. Rapa exerts its apoptotic effect via a reversible binding to the cytosolic receptor protein FKBP-12, as demonstrated in competition experiments with FK506, which is structurally related to Rapa. Partial inhibition of Rapa-induced apoptosis was obtained by addition of ZVAD-fmk, which implies caspase-dependent and caspase-independent processes. The fact that Rapa exerts a specific effect on DCs but not on monocytes and macrophages might contribute to the unique actions of Rapa in the prevention of allograft rejection and other immune responses.

L3 ANSWER 25 OF 49 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 2001185405 MEDLINE
DOCUMENT NUMBER: 21172659 PubMed ID: 11274753
TITLE: Acute graft-vs-host disease: pathobiology and management.
COMMENT: Erratum in: Exp Hematol 2001 May;29(5):653
AUTHOR: Goker H; Haznedaroglu I C; Chao N J
CORPORATE SOURCE: Bone Marrow and Stem Cell Transplantation Program, Duke University Medical Center, Durham, NC 27705, USA.
SOURCE: EXPERIMENTAL HEMATOLOGY, (2001 Mar) 29 (3) 259-77. Ref: 215
Journal code: 0402313. ISSN: 0301-472X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010502
Last Updated on STN: 20010716
Entered Medline: 20010426

AB Acute graft-vs-host disease (GVHD) is a major obstacle to safe allogeneic hematopoietic stem cell transplantation (HSCT), leading to a significant morbidity and mortality. GVHD occurs when transplanted donor T lymphocytes react to foreign host cells. It causes a wide variety of host tissue injuries. This review focuses on the pathobiological basis, clinical aspects, and current management strategies of acute GVHD. Afferent phase of acute GVHD starts with myeloablative conditioning, i.e., before the infusion of the graft. Total-body irradiation (TBI) or high-dose chemotherapy regimens cause extensive damage and activation in host tissues, which release inflammatory cytokines and enhance recipient major histocompatibility complex (MHC) antigens. Recognition of the foreign host antigens by donor T cells and activation, stimulation, and proliferation of T cells is crucial in the afferent phase. Effector phase of acute GVHD results in direct and indirect damage to host cells. The skin, gastrointestinal tract, and liver are major target organs of acute GVHD. Combination drug prophylaxis in GVHD is essential in all patients undergoing allogeneic HSCT. Steroids have remained the standard for the treatment of acute GVHD. Several clinical trials have evaluated monoclonal antibodies or receptor antagonist therapy for steroid-resistant acute GVHD, with different successes in a variety of settings. There are some newer promising agents like mycophenolate mofetil, glutamic acid-lysine-alanine-tyrosine (GLAT), **rapamycin**, and trimetrexate currently entering in the clinical studies, and other agents are in development. Future experimental and clinical studies on GVHD will shed further light on the better understanding of the disease pathobiology and generate the tools to treat malignant disorders with allogeneic HSCT with specific graft-vs-tumor effects devoid of GVHD.

L3 ANSWER 18 OF 49 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:833124 CAPLUS
DOCUMENT NUMBER: 135:356762
TITLE: Targeting phagocytosis of apoptotic cells for cross-presentation of antigens in MHC class I pathway
INVENTOR(S): Albert, Matthew; Birge, Raymond; Jesathesan, Mithila; Darnell, James E.
PATENT ASSIGNEE(S): The Rockefeller University, USA
SOURCE: PCT Int. Appl., 147 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001085207	A2	20011115	WO 2001-US14796	20010507
WO 2001085207	A3	20020711		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002004041	A1	20020110	US 2001-804584	20010312

PRIORITY APPLN. INFO.:
US 2000-545958 A 20000505
US 2001-804584 A2 20010312
US 1999-251896 A2 19990219

AB The authors disclose methodol. for modulating the cellular immune response to a pre-selected antigen, either ex vivo or in vivo, whereby **dendritic** cell maturation is permitted to occur in the absence (or presence) of effective CD4+ T-cell help. The authors also disclose that phagocytosis by **dendritic** cells was mediated via .beta.5-integrin. In one example, the authors demonstrate that an anti-influenza cytotoxic T-cell response was enhanced on incubation of syngeneic T-cells with **dendritic** cells and apoptotic monocytes infected with influenza A virus. In a second related example, anti-influenza cytotoxic T-cell response was suppressed on incubation of syngeneic CD8+ T-cells with **dendritic** cells in the absence of T-cell help.

L3 ANSWER 17 OF 49 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
ACCESSION NUMBER: 2002-07018 BIOTECHDS
TITLE: Modulating antigen processing, useful for treating an autoimmune disease, e.g. psoriasis, Crohn's disease, arthritis, multiple sclerosis or lupus, by genetically modifying phagocytes to express apoptotic-cell receptors; recombinant vector expression in host cell, genetically engineered non-human cell and antibody for disease gene therapy
AUTHOR: ALBERT M; BIRGE R; JESATHESAN M; DARNELL J E
PATENT ASSIGNEE: UNIV ROCKEFELLER
PATENT INFO: WO 2001085207 15 Nov 2001
APPLICATION INFO: WO 2000-US14796 5 May 2000
PRIORITY INFO: US 2001-804584 12 Mar 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-082876 [11]
AN 2002-07018 BIOTECHDS
AB DERWENT ABSTRACT:

L3 ANSWER 4 OF 49 BIOTECHDS COPYRIGHT 2003 THOMSON DERWENT AND ISI
ACCESSION NUMBER: 2002-11647 BIOTECHDS
TITLE: Use of **rapamycin** and a gene therapy vector to inhibit immune response of a host to a gene therapy vector and encoded transgene product;
adeno virus vector-mediated gene transfer and expression in host cell for Gaucher disease, Fabry syndrome, Niemann-Pick B disease, Hunter disease, Morquio disease, Maroteaux-Lamy disease, Pompe disease, Hurler-Scheie diseaseor hemophilia therapy
AUTHOR: SCARIA A
PATENT ASSIGNEE: SCARIA A
PATENT INFO: US 2002014242 7 Feb 2002
APPLICATION INFO: US 2000-876574 31 Jul 2000
PRIORITY INFO: US 2001-876574 7 Jun 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-215914 [27]
AN 2002-11647 BIOTECHDS
AB DERWENT ABSTRACT:

L42 ANSWER 3 OF 28 PCTFULL COPYRIGHT 2003 Univentio
ACCESSION NUMBER: 1998010056 PCTFULL ED 20020514
TITLE (ENGLISH): TREATMENT OF ANTIGEN PRESENTING CELLS TO MODULATE ANTIGEN PRESENTING CELL FUNCTION
TITLE (FRENCH): TRAITEMENT DE CELLULES PRESENTANT L'ANTIGENE POUR MODULER LA FONCTION DE CELLULES PRESENTANT L'ANTIGENE
INVENTOR(S): BROOKS, Stephen, P.; TOMASI, Thomas, B.; BERNSTEIN, Zale, P.
PATENT ASSIGNEE(S): HEALTH RESEARCH INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9810056	A1	19980312
DESIGNATED STATES	AU CA JP KP KR NZ AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE		
APPLICATION INFO.:	**WO 1997-US15431**	**A**	**19970902**
PRIORITY INFO.:	US 1996-60/025,332		19960903
	US 1997-60/025,332		19970829

AI **WO 1997-US15431** **A 19970902**

DETD There are several pathological conditions in which T-cell proliferation/ stimulation is **suppressed**, and in which the allo-stimulatory accessory cell function may be inhibited. These conditions include, but are not limited to inflammation, inflammatory diseases (e.g., inflammatory. . . immune response mediated by T-cells in HIV seropositive individuals is depressed or absent. This loss of T-cell stimulatory function of APCs (accessory cells, **dendritic** cells, and macrophages), has been reported by some groups to accompany HIV infection and has been hypothesized to be one of the primary mechanism by which the virus induces the **suppression** of systemic immunity which defines AIDS. The reduction in the number of **CD4+** T-cells, loss of recall antigen response, and the failure to properly respond to infectious disease, have all been linked to virally compromised accessory. . .

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ACCESSION NUMBER: 1997037687 PCTFULL ED 20020514
TITLE (ENGLISH): NOVEL PRODUCT AND PROCESS FOR T LYMPHOCYTE VETO
TITLE (FRENCH): PRODUIT ET PROCEDE NOUVEAUX POUR MOLECULES VETO DES LYMPHOCYTES T
INVENTOR(S): STAERZ, Uwe, D.
PATENT ASSIGNEE(S): NATIONAL JEWISH CENTER FOR IMMUNOLOGY AND RESPIRATORY MEDICINE; STAERZ, Uwe, D.
LANGUAGE OF PUBL.: English
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	WO 9737687	A1	19971016

DESIGNATED STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU GH KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.:	**WO 1997-US5943**	**A**	**19970410**
PRIORITY INFO.:	US 1996-8/630,172		19960410
AI	**WO 1997-US5943**	**A**	**19970410**

DETD . . . such a manner that the responding cell is either activated,, anergized or killed, Traditional stimulator cells include professional antigen presenting cells (APC; e.g., **dendritic** cells, macrophages and B cells), According to the present invention, stimulator cells can also include a cell having a T cell veto. . . to herein as a T cell),
A responding cell includes any cell capable of being activated by a stimulator cell, Traditional responding cells include **CD4**-CD8+ (CD8+), **CD4**+CD8+1 **CD4** -CD8-1 **CD4**+CD8- (**CD4**+) w a@ and y6 T cells, According to the present invention, responding cells can also include B lymphocytes (also referred to herein. . . measuring cell death (e,g, apoptosis assays). Pref erably, a responding cell of the present invention includes a T cell, in particular a naive **CD4**+ or CD8+ T cell,
Activation of a responding cell refers to induction of signal transduction pathways in the responding cell resulting in production of cellular products (e.g., interleukin-2) by that cell. **Anergy** refers to the diminished reactivity by a responding cell,
Embodiments of the present invention include a novel T cell veto molecule having at. . .

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ACCESSION NUMBER: 1998010056 PCTFULL ED 20020514
TITLE (ENGLISH): TREATMENT OF **ANTIGEN PRESENTING** CELLS TO MODULATE **ANTIGEN PRESENTING** CELL FUNCTION
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TIEN TREATMENT OF **ANTIGEN PRESENTING** CELLS TO MODULATE **ANTIGEN PRESENTING** CELL FUNCTION

AI **WO 1997-US15431 A 19970902**

ABEN Provided herein is the discovery of a novel mechanism by which the ability of **antigen** **presenting** cells to stimulate T-cell function is inhibited by the formation of immunosuppresive complexes comprising the **antigen presenting** cell membrane-associated 'beta'glycan and cytokine TGF-'beta'. Also provided are methods for restoring T-cell stimulatory function of **antigen** **presenting** cells of an individual, having such function suppressed by 'beta'glycan-TGF-'beta' complex formation, by either removing TGF-'beta' from the cell surface of the **antigen presenting** cells, removing 'beta'-glycan or 'beta'glycan complexed to TGF-'beta' from the cell surface of the **antigen presenting** cells, or by contacting the **antigen presenting** cells with one or more **antigen** **presenting** cell activating factors which overcome the suppression of the T-cell stimulatory function of **antigen presenting** cells.

DETD TGF-O mediated immunosuppression is believed to play a role in several pathological conditions. Tumors that actively secrete TGF-fl can inhibit or **suppress** **CD4+** helper T cell activity, wherein such suppression can be overcome by the addition of neutralizing antibodies to TGF-fl (Ruscetti et al., 1993, supra).. . .

Thus, there is a need to identify and overcome defects in APCs, and/or TGF-0 mediated **suppression** of **CD4+** helper T cell activity, observed in pathological conditions. Methods for overcoming such defects and/or

suppression offers new therapeutic approaches for these pathologic conditions.

It is another object of the present invention to provide methods directed to overcoming TGF-0 mediated **suppression** of **CD4**+ helper T cell activity observed in certain pathological conditions.

. . .

invention to provide in vitro methods for overcoming defects in or the loss of T-cell stimulatory function of APCs, and/or overcoming TGF-fl mediated **suppression** of **CD4**+ helper T cell activity, observed in certain pathological conditions.

. . .

invention to provide in vivo method for overcoming defects in or the loss of T-cell stimulatory function of APCs, and/or overcoming TGF-# mediated **suppression** of **CD4**+ helper T cell activity, observed in certain pathological conditions.

. . .

mean either or collectively all, of the three mammalian isotypes including TGF-01, TGF-02, and TGF-#3, as all three isotypes have been shown to **suppress** the APC function of stimulating **CD4**+ helper T cell activity.

. . .

and anti-Oglycan antibody)

EXAMPLE 1

This example illustrates that (a) the flglycan on APCs binds to TGF-fl; and (b) the APC function of stimulating **CD4**+ helper T cell activity is **suppressed** or inhibited by the binding of TGF-O to Oglycan. The mechanism of TGF-fl suppression of APC function was characterized by using two well. . .

. . .

that antigen presenting cells express flglycan on their cell surface; that Oglycan on APCs binds to TGF-0; that APC function of stimulating **CD4**+ helper T cell activity is **suppressed** or inhibited by the

binding of TGF-O to flglycan; that TGF-O:#glycan complexes can be enzymatically removed from the cell surface of. . .